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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07K 5/00, 5/08, A61K 38/05 | A1

(11) International Publication Number: **WO 98/50420**

(43) International Publication Date: 12 November 1998 (12.11.98)

(21) International Application Number: PCT/EP98/02587

(22) International Filing Date: 28 April 1998 (28.04.98)

(30) Priority Data:
97201286.8 2 May 1997 (02.05.97) EP

(34) Countries for which the regional or international application was filed: NL et al.

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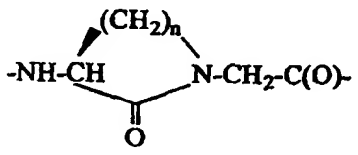
(81) Designated States: AM, AU, BB, BG, BR, CA, CN, CZ, EE, GE, HU, ID, IS, JP, KG, KP, KR, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, TT, UA, US, UZ, VN, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: SERINE PROTEASE INHIBITORS



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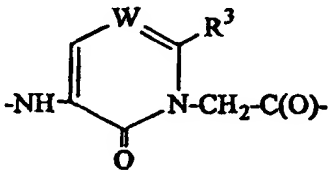

(II)

(57) Abstract

The invention relates to a compound having the formula (I): R^1SO_2–B–X–Z–C(O)–Y, B is a bond, an amino acid of the formula –NH–CH[$(CH_2)_p$C(O)OH]–C(O)– or an ester derivative thereof wherein p is 1, 2, or 3, Gly, D–1–Piq, D–3–Piq, D–1–Tiq, D–3–Tiq, D–Atc, Aic, or a L– or D–amino acid having a hydrophobic, basic or neutral side chain; X is an amino acid with a hydrophobic side chain, glutamine, serine, threonine, a cyclic amino acid optionally containing an additional heteroatom selected from N, O or S, and optionally substituted with (1–6C)alkyl, (1–6C)alkoxy, benzyloxy or oxo, or X is 2–amino–isobutyric acid, –NR^2–CH_2–C(O)– or the fragment (I) or (II), wherein n is 2, 3, or 4, W is CH or N and R^3 is H, (1–6C)alkyl or phenyl which groups may optionally be substituted with hydroxy, (1–6C)alkoxy, COOH, COO(1–6C)alkyl, $CONH_2$, or halogen; Z is lysine or 4–aminocyclohexylglycine. The compounds of the invention have anticoagulant activity and can be used in treating or preventing thrombin–related diseases. The variable R^1 and Y are defined in claim 1.

Table 44 : Characterization (retention time on reversed phase HPLC and M+H peak in electrospray mass spectrometry) of $EtSO_2$-B-X-LysΨ[COCO]-O-iPropyl prepared on Hydroxymethyl-resin. HPLC conditions : Flow : 1.0 mL/min ; Buffers A : water, B : acetonitril/water (6/4 v/v), C : 0.5 M phosphate-buffer pH = 2.1 ; Gradient : 0 → 45 min 65 % A/15 % B/20 % C → 0 % A/80 % B/20 % C. UV-detection at 210 nm.

	B				
	Asn	**D-Leu**	**D-Phe**	**Nal**	**D-3-Tiq**
$EtSO_2$-B-D-Leu-D/L-LysΨ[COCO]-O-iPropyl	Rt = 17.07 min M+H = 536.4	Rt = 27.20 min M+H = 535.6	Rt = 30.89 min M+H = 569.4	Rt = 38.17 min M+H = 619.6	Rt = 33.54 min M+H = 581.4
$EtSO_2$-B-Leu-D/L-LysΨ[COCO]-O-iPropyl	Rt = 17.17 min M+H = 536.4	Rt = 30.78 min M+H = 535.6	Rt = 32.89 min M+H = 569.4	Rt = 37.79 min M+H = 619.6	Rt = 33.60 min M+H = 581.4
$EtSO_2$-B-Gln-D/L-LysΨ[COCO]-O-iPropyl	Rt = 5.40 min M+H = 551.2	Rt = 15.74 min M+H = 550.4	Rt = 18.05 min M+H = 584.4	Rt = 28.44 min M+H = 634.4	Rt = 21.27 min M+H = 596.4
$EtSO_2$-B-Phe-D/L-LysΨ[COCO]-O-iPropyl	Rt = 20.75 min M+H = 570.4	Rt = 33.33 min M+H = 569.4	Rt = 35.18 min M+H = 603.4	Rt = 39.47 min M+H = 653.6	Rt = 35.92 min M+H = 615.6

Example 45.

The following compounds can be prepared by using the methods of the present invention:

CF_3SO_2-D-Cha-Pro-LysΨ[COCO]-O-iPropyl

$MeSO_2$-D-Tyr(Me)-Pro-LysΨ[COCO]-O-iPropyl

n-ButylSO_2-D-Tyr(Me)-Pro-LysΨ[COCO]-O-iPropyl

CF_3SO_2-D-Tyr(Me)-Pro-LysΨ[COCO]-O-iPropyl

$BzlSO_2$-D-Tyr(Me)-Pro-LysΨ[COCO]-O-iPropyl

$EtSO_2$-D-(p-OEt-Phe)-Pro-LysΨ[COCO]-O-iPropyl

$EtSO_2$-D-Nle-Pro-LysΨ[COCO]-O-iPropyl

$EtSO_2$-D-Cha-Azt-LysΨ[COCO]-O-iPropyl

$EtSO_2$-D-Cha-(N-cyclopentyl-Gly)-LysΨ[COCO]-O-iPropyl

$EtSO_2$-D-Cha-Val-LysΨ[COCO]-O-iPropyl

$EtSO_2$-D-Cha-Pec-LysΨ[COCO]-O-iPropyl

$EtSO_2$-D-Cha-(3,4-dehydro-Pro)-LysΨ[COCO]-O-iPropyl

$EtSO_2$-D-Cha-Pro-LysΨ[COCO]-Azetidine

$MeSO_2$-D-Cha-Pro-LysΨ[COCO]-Azetidine

n-ButylSO_2-D-Cha-Pro-LysΨ[COCO]-Azetidine

CF_3SO_2-D-Cha-Pro-LysΨ[COCO]-Azetidine

BzlSO_2-D-Cha-Pro-LysΨ[COCO]-Azetidine

[3-(BzlSO_2amino)-2-oxo-1,2-dihydropyridinyl]-acetyl-LysΨ[COCO]-Azetidine

[3-(BzlSO_2amino)-6-methyl-2-oxo-1,2-dihydropyridinyl]-acetyl-LysΨ[COCO]-Azetidine

$MeSO_2$-D-Cha-Pro-AcgΨ[COCO]-O-iPropyl

n-ButylSO_2-D-Cha-Pro-AcgΨ[COCO]-O-iPropyl

CF_3SO_2-D-Cha-Pro-AcgΨ[COCO]-O-iPropyl

BzlSO_2-D-Cha-Pro-AcgΨ[COCO]-O-iPropyl

$EtSO_2$-D-Tyr(Me)-Pro-AcgΨ[COCO]-O-iPropyl

$MeSO_2$-D-Tyr(Me)-Pro-AcgΨ[COCO]-O-iPropyl

n-ButylSO_2-D-Tyr(Me)-Pro-AcgΨ[COCO]-O-iPropyl

CF_3SO_2-D-Tyr(Me)-Pro-AcgΨ[COCO]-O-iPropyl

BzlSO_2-D-Tyr(Me)-Pro-AcgΨ[COCO]-O-iPropyl

$EtSO_2$-D-Tyr(Et)-Pro-AcgΨ[COCO]-O-iPropyl

$EtSO_2$-D-Nle-Pro-AcgΨ[COCO]-O-iPropyl

$EtSO_2$-D-Cha-Azt-AcgΨ[COCO]-O-iPropyl

$EtSO_2$-D-Cha-(N-cyclopentyl-Gly)-AcgΨ[COCO]-O-iPropyl

$EtSO_2$-D-Cha-Val-AcgΨ[COCO]-O-iPropyl

$EtSO_2$-D-Cha-Pec-AcgΨ[COCO]-O-iPropyl

$EtSO_2$-D-Cha-(3,4-dehydro-Pro)-AcgΨ[COCO]-O-iPropyl

$EtSO_2$-D-Cha-Pro-AcgΨ[COCO]-Azetidine

$EtSO_2$-D-Tyr(Me)-Pro-AcgΨ[COCO]-Azetidine

$EtSO_2$-D-Tyr(Me)-Pro-AcgΨ[COCO]-NH_2

$MeSO_2$-D-Cha-Pro-AcgΨ[COCO]-Azetidine

n-ButylSO_2-D-Cha-Pro-AcgΨ[COCO]-Azetidine

CF_3SO_2-D-Cha-Pro-AcgΨ[COCO]-Azetidine